DIGITALIS GLYCOSIDE SERUM ASSAY UTILIZATION AND INTERPRETATION

by

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INTRODUCTION

In recent years, significant advances were made in the determination of optimal therapeutic dosage regimens for many drugs. Perhaps the main thrust in this area has been in the development of sensitive assay techniques allowing effective selection of dosage regimens on the basis of pharmacokinetic and biopharmaceutic knowledge. This has resulted in more accurate dosage selection with concomitant improvement in therapy and decreased incidence of adverse effects.[1] Furthermore, the availability of serum assays for drugs has made it possible to maintain drug concentration in a therapeutic range for longer periods of time without risking the danger of serious toxicity,[2,3] or subtherapeutic effect.[4] This is especially important for those drugs having a narrow therapeutic index and a highly variable half-life such as that seen with the digitalis glycosides.

Digitalis glycoside serum assay utilization at its inception was low. However, as techniques of measurement improved and became increasingly more available, the frequency with which digitalis glycoside assays are ordered has dramatically risen.[1,5] With this increase, much confusion has developed concerning assay interpretation resulting in severe criticism of the clinical utility of digitalis glycoside assays.[5,6,7,8]

The interpretation of digitalis glycoside serum assays requires an appreciation of laboratory methodology,[9-12] interpatient variability in

pharmacologic response,[19] as well as the patient's disease state,[13-18] age, sex and body size.[20] Most clinical symptoms of digitalis toxicity are nonspecific and should therefore be interpreted accordingly.[1,4,21]

Laboratory values such as serum potassium, calcium, magnesium, oxygen tension and pH also play important roles in the evaluation of patient response to digitalis glycosides.[19] Appraisal of patient compliance is necessary for adequate assessment of therapy with digitalis glycosides.[22] Numerous drug interactions may have a significant bearing on therapeutic success with digitalis glycosides and should therefore be considered.[19] In addition, misunderstanding of pharmacokinetic principles and their application can further complicate the assessment of a patient's clinical status.[23]

Error in the utilization of assays is more apt to occur when such a large variety of factors must be considered. A study with digitalis glycoside assays has recently revealed significant deficiencies in the area of appropriateness of assay indication and interpretation, and in the appropriateness of dosage adjustments following assay reports.[8] Similar findings are reported with other drugs.[24,25]

It was the purpose of the present study to examine some of these problems with regard to the use of digitalis glycoside serum assays as they occur in a semi-private hospital setting. The study was designed to gain additional knowledge in the following areas: a) frequency of assay utilization, b) appropriateness of assay indication, c) appropriateness of assay use as measured by blood sampling time, d) actual assay levels, e) appropriateness of dosage adjustments, f) patient costs and g) physician understanding of digitalis glycoside assay utilization.

METHODS

The study was performed over 35 consecutive days in a semi-private 350 bed hospital located in Salt Lake City, Utah. The hospital was staffed by both resident and private physicians. Criteria for exclusion of physicians from the study include prior knowledge of the study or lack of cooperation in the study.

Data Collection

All requests for inpatient digitalis glycoside assays were received by Nuclear Medicine technicians who recorded code number, date, time received in laboratory, patient name, patient hospital number, patient room number, cost to patient and the serum level which was determined using the DIGI-TAB Radioimmunoassay Digoxin Diagnostic Kit developed by Nuclear Medical Laboratories, Inc., Dallas, Texas. This information, with the exception of the actual serum level, was given to the investigator who reviewed all patient charts for information affecting assay use and interpretation (Appendix A). All data were collected between 12 and 24 hours after the time of the initial request, thus allowing physicians sufficient time for recording information. Informed written consent was obtained from each patient.

If electrocardiograms (ECG) were ordered within 48 hours previous to the time of the initial assay request, they were photocopied. Other baseline ECGs were photocopied as well, if they were found in the chart.

The ECGs and a copy of the corresponding Patient Data Collection sheet were sent to another hospital for independent interpretation by two board certified cardiologists. Both cardiologists were blinded to patient names, physician names and the hospital name. Each rated all patients' ECGs with an overall evaluation of Toxic, Possibly Toxic, Probably Non-Toxic and Non-Toxic, corresponding to scores of 4, 3, 2 and 1 respectively. Each cardiologist worked independently and was unaware of interpretations by the other. Inter-rater reliability was measured by the Pearson Product-Moment Correlation Formula.[26]

A theoretical dose was calculated for each patient where possible using Jelliffe's equation:[20]

$$\text{Maintenance Dose} = (\text{Total Body Stores}) \frac{14 + \frac{\text{Creatinine Clearance}}{5}}{100}$$

This dose was then compared to the actual dosage which was received to allow for evaluation of the appropriateness of the current regimen (Appendix B).

Creatinine clearance was estimated using the Siersback-Nielson nomogram.[27] Serum potassium, oxygen tension and pH values ordered within 48 hours previous to the time of the initial request for serum assays were obtained from the chart. The most recent values of serum calcium, magnesium, creatinine and blood urea nitrogen were recorded if these laboratory values were obtained during each patient's current admission. Laboratory values ordered after the time of the original request for digitalis glycoside assays were not recorded.

A complete problem list from each patient chart as well as the indication for digitalis glycoside therapy, current dosage regimen, most recent dosage change and the exact time of the most recent dose received prior to serum sampling were obtained when available. All medications received in the hospital and medications taken at home within three months prior to admission were recorded as obtained from the patient's chart.

Evidence of toxicity was obtained from the chart in three categories: 1) Gastrointestinal symptoms, 2) Central nervous symptoms, and 3) Visual symptoms (Appendix A).

Evidence of subtherapeutic effect was obtained as recorded in the patient's chart in two categories: 1) Symptoms of disease state deterioration, and 2) Compliance history (Appendix A). Compliance was recorded as being excellent, good, fair or poor corresponding to the number of doses missed per month equal to: a) one or less, b) two, c)three or d) greater than three, respectively. Poor compliance histories received Clinical Evaluation Point System scores of minus one as discussed below (Appendix B). Adjustments made in therapy following the appearance of assay results in the chart were noted on the Patient Data Collection Sheet. Digitalis glycoside therapy was recorded as increased, decreased or not changed.

At the end of the five weeks, each physician was interviewed by telephone using a questionnaire (Appendix C). The investigator used an identical explanation when discussing its purpose with all physicians interviewed (Appendix D). Physicians were not permitted to discuss the questions with the investigator. Only the re-reading of questions to the physicians was allowed.

Evaluation

The frequency of availability of each piece of information that may be used for clinical evaluation of patients was determined. Each assay was assigned a score according to a standardized clinical evaluation system.(Appendix B). A score of 10 or more was interpreted as a reasonable indication for the assay on the grounds of suspected toxicity. A score of -10 or less was interpreted as a reasonable indication for the assay on the grounds of suspected subtherapeutic effect. A score from minus nine to nine was interpreted as an unreasonable indication for the assay due to a high likelihood that the serum level would be within the therapeutic range and would probably not benefit the patient in the form of indicated alterations in therapy. The scores were recorded and compared to actual serum level reports. The reliability of this method in predicting assay results was then assessed.

The actual adjustment in therapy ordered following assay results was compared to: a) therapy which patients would have received following ideal clinical assessment alone, and b) therapy which patients would have received under ideal clinical assessment with assay results.

Therapy which patients would have received following ideal clinical assessment alone is defined as that therapy required for correction of the clinical evaluation score to within normal limits (WNL). In other words, if the patient scored in the toxic range, the dosage shoud be decreased; if the patient scored in the subtherapeutic range, the dosage should be increased; and, if the patient scored within normal limits, the dosage should not be changed.

The therapy which patients would have received following ideal clinical assessment with assay results was determined on the basis of clinical and laboratory information (Appendix E).

A patient cost analysis was then performed based on the current rates. Annual estimations of patient losses were made on the basis of this five week period.

Finally, the physicians' quiz was scored (Appendix C).

RESULTS

Over a period of 35 days, 29 physicians requested 107 digoxin and four digitoxin assays for 70 inpatients. One patient had a total of 20 assays performed during the period of this study. Of the 111 total assays performed, 27 physicians, 101 assays and 68 patients qualified for entry into this study. Ten physicians were residents. The remaining 17 were in private practice. Resident signatures appeared on 70 assay requests while 31 requests were signed by physicians in private practice. The range of patient ages was from 35 to 90 years. Ninety percent of all patients were at least 60 years of age.

Data were available for 10 of 11 factors that may be used for clinical evaluation of digitalis toxicity. The frequency of availability of this information in patient charts is shown in Table I.

TABLE I: Frequency of Available Information in Patient Charts

	Frequency of Availability
Problem List	94%
Medication History	89%
Potassium	88%
Indication for Digitalis Glycosides	84%
Regimen Prior to Admission	82%
Serum Creatinine/Blood Urea Nitrogen	79%
Evidence of Toxicity and/or Non-Compliance	77%
Electrocardiogram	52%
Calcium	50%
pO_2/pH	33%
Magnesium	0%

Fifty-two patients had electrocardiograms available at the time of assay request, and all were rated by the two cardiologists. Reliability of their ratings was 0.78 as assessed by the Pearson Product-Moment Correlation Formula[26] and is considered to be adequate by this method. The ratings by each cardiologist are shown in Table II.

TABLE II: Electrocardiogram Rating Summary by Two Cardiologists

	Possibly Toxic	Toxic	Other
Cardiologist A	11	0	41
Cardiologist B	11	2	39

In the clinical evaluation of assay necessity (Table III), 45 assays (44.5 percent) scored from minus nine to nine points and were deemed unnecessary assays, or within normal limits (WNL). Twenty-two of these (50 percent) had scores of zero. A total of 56 assays (55.4 percent) were deemed necessary by the scoring system. Forty-six assays received clinical evaluation scores of 10 or more for a toxic rating. Ten assays received clinical evaluation scores of -10 or less for a subtherapeutic rating. It should be noted that patient number six had a total of 20 assays performed. Of these, 13 assays scored in the toxic range by the Clinical Evaluation System. However, 10 of the 13 assays were ordered on a daily basis and were therefore unable to give any beneficial or needed information that could alter the patient's overall therapy. Consequently, a more accurate estimation of necessary assays would be 45.5 percent.

Thirteen assays were obtained less than six hours after the previous dosage, thus not allowing proper distribution to take place.[23] Although Jisalo[23] recommends an eight hour minimum, two additional

samples were obtained less than eight hours after the previous dosage. One physician requested a specific time for serum sampling for a single assay.

TABLE III: Results of Clinical Evaluation System for Assay Necessity

	Toxic	WNL	Subtherapeutic
Number of Assays	46	45	10

A total of 22 assays was reported greater than or equal to 2.2 ng/ml for digoxin. Eight assays for digoxin were reported greater than or equal to 3.0 ng/ml. None of the four digitoxin assays reported in this study was in the toxic range. Non-toxic ranges by our laboratory methods are regarded as below 2.2 ng/ml for digoxin and below 45 ng/ml for digitoxin.

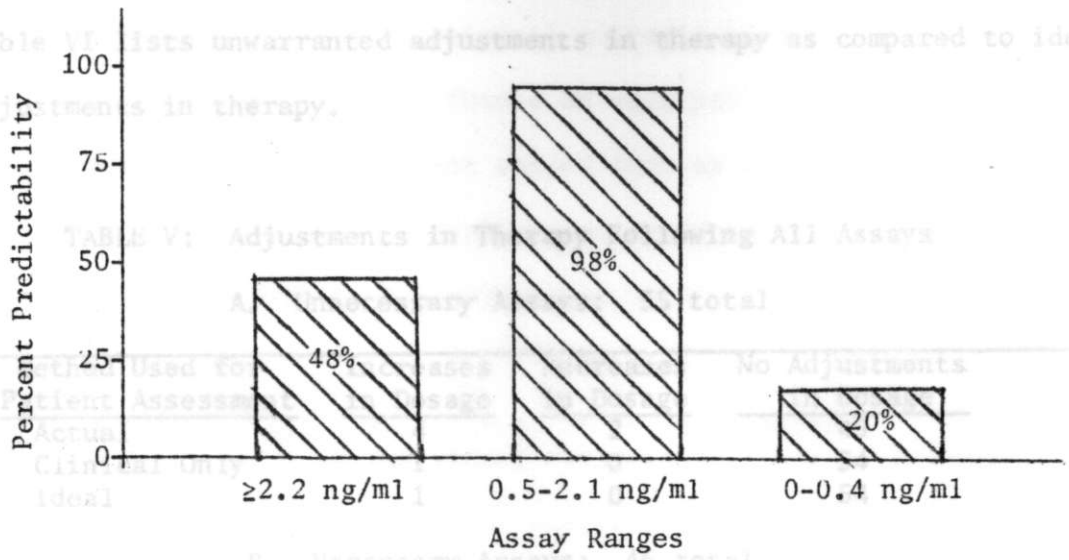
Assay results are compared to clinical evaluation scores in Table IV. The utility of the Clinical Evaluation Score is presented in Figure 1. Ninety-eight percent of digoxin assay reports were predictably in the therapeutic range of 0.5 to 2.1 ng/ml. Toxic and subtherapeutic concentration ranges were not predictable by this method.

TABLE IV: Clinical Evaluation in Comparison with Assay Results for Digoxin

Assay Results (ng/ml)	46 Assays ≥10 Points* Toxic	45 Assays 0-9 Points* WNL†	10 Assays ≤-10 Points* Subtherapeutic
≥2.2	48.8%	0%	10%
0.5-2.1	45.6%	98%	70%
0-0.4	4.7%	2%	20%

*See Appendix D for Clinical Evaluation Scoring System
†Within Normal Limits

FIGURE 1: Predictability of Assay Reports Using a Clinical Evaluation Scoring System



Evaluation of the appropriateness of therapy is reported in two categories: 1) Adjustments in therapy following all assays (Table V), and 2) Unwarranted adjustments in therapy (Table VI). Both categories are divided into unnecessary and necessary assays, corresponding to clinical evaluation scores of minus nine to nine, or less than or equal to -10, or greater than or equal to 10, respectively. Tables V and VI are further subdivided into: a) actual adjustment in therapy that patients received, b) clinical adjustment in therapy that patients would have received had there been no digitalis glycoside assays available, and c) ideal adjustment in therapy that patients should have received based on proper interpretation of both clinical presentation and serum assay results.

Table V lists the total numbers of adjustments in dosage for each of the three methods used for patient assessment. However, disparity between the methods can be seen on closer evaluation of either the total

numbers of warranted adjustments or the total numbers of unwarranted adjustments that were made in therapy when compared to ideal adjustments. Table VI lists unwarranted adjustments in therapy as compared to ideal adjustments in therapy.

TABLE V: Adjustments in Therapy Following All Assays

A. Unnecessary Assays: 55 total

Method Used for Patient Assessment	Increases in Dosage	Decreases in Dosage	No Adjustments in Dosage
Actual	4	2	49
Clinical Only	1	0	54
Ideal	1	0	54

B. Necessary Assays: 46 total

Method Used for Patient Assessment	Increases in Dosage	Decreases in Dosage	No Adjustments in Dosage
Actual	9	6	31
Clinical Only	12	33	1
Ideal	12	18	16

TABLE VI: Unwarranted Adjustments in Therapy

A. Unnecessary Assays: 55 total

Method Used for Patient Assessment	Increases in Dosage	Decreases in Dosage	No Adjustments in Dosage	Totals
Actual	2	2	0	4
Clinical Only	0	0	0	0

B. Necessary Assays: 46 total

Method Used for Patient Assessment	Increases in Dosage	Decreases in Dosage	No Adjustments in Dosage	Totals
Actual	3	1	16	20
Clinical Only	3	15	0	18

Of the 55 unnecessary assays obtained, four (7.3 percent) resulted in unwarranted adjustments in dosage. There were no unwarranted adjustments recommended with the use of clinical criteria alone. Of the 46

necessary assays obtained, 20 (43 percent) resulted in unwarranted adjustments in dosage. This compared with 18 (39 percent) unwarranted adjustments with the use of clinical criteria alone.

The number of assays performed on each patient varied (Table VII). Consequently, costs per patient ranged from as little as $17.50 to as much as $560.00 for digitalis glycoside assay service alone. A patient cost analysis appears in Table VIII.

TABLE VII: Frequency of Assay Performance on Individual Patients

Number of Assays Performed on Each Patient	Number of Patients Receiving this Number of Assays	Percent of Total Patients
1	54	79%
2	12	18%
3	1	1.5%
20	1	1.5%

TABLE VIII: Patient Cost Analysis* Based on Frequency Occuring in this Five Week Period

Assay Charge Category	Cost per Category	Categories per year	Projected Annual Patient Costs
Standard Digoxin	$25.75	1084.6	$27,928.45
Standard Digitoxin	30.99	41.7	1,251.00
Stat Digoxin/Digitoxin	44.10	41.7	1,838.97
Late Stat Digoxin/Digitoxin	10.00	62.6	626.00
		TOTAL =	$31,644.42

*Based on current hospital rates in effect by the end of this study.

Annual patient losses may approximate $17,250 as calculated by the equation:

Losses = (% Unnecessary Assays) (Annual Patient Costs)

A summary of selected physician quiz results appears in Table IX. Quiz performance was approximately the same for both groups of physicians and could not be correlated to rationale in ordering assays or to frequency of use.

TABLE IX: Summary of Physician Quiz Results for Selected Questions*

Question Number	Question Content	Resident M.D. Scores (10 quizzes)	Private M.D. Scores (12 quizzes)	All Physicians Scores (22 quizzes)
4	Digoxin half-life	35%	4%	18%
5	Digoxin serum sampling time	20%	67%	46%
7	Digoxin assay costs to patient	20%	42%	32%
10	Objective dosing techniques	0%	0%	0%

*See Appendix B for full questions and scoring system. Appendix F is a comprehensive summary of results.

Although the knowledge and understanding of half-life information play key roles in optimally utilizing results supplied by serum assay for any drug,[1,5,6] only 18 percent of all physicians in this study appeared to be knowledgeable in this area. Thirty-five percent of residents responded correctly while less than four percent of physicians in private practice could answer this question.

Physicians in private practice appeared to be more aware of the proper timing necessary for ordering digoxin assays. This was seen by their performance both on the quiz and in clinical results. Physicians in private practice scored a mean of 67 percent on this question (number five in Table IX) versus mean resident scores of 20 percent. Fifty percent of the resident physicians requested 77 percent of assays that were ordered less than six hours after previous dosages, whereas only

18 percent of the private physicians ordered 23 percent of assays before the six hour limit. However, it should be borne in mind that signatures of residents do not necessarily reflect their own decisions.

Nearly 70 percent of all physicians interviewed had no idea what assay costs were to the patient. Eighty percent of residents and 58 percent of the private physicians were unaware of the costs involved.

Also noteworthy is the fact that none of the 23 physicians interviewed used an objective technique for dosage determination. All of them determined dosages from clinical judgment despite the fact that there now exist several more objective methods for doing so.[28]

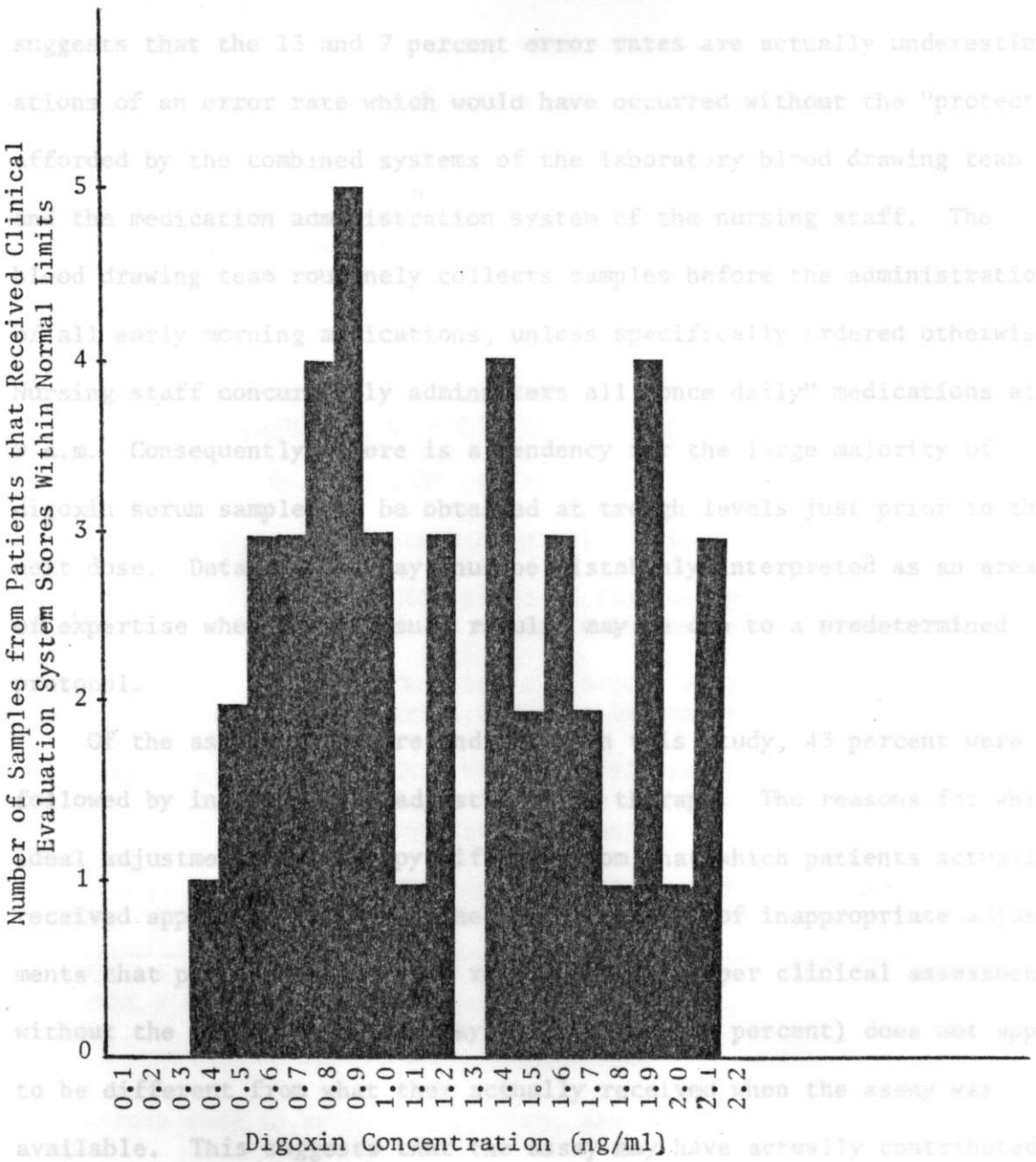
DISCUSSION

The frequency of assay utilization in this hospital seemed to be approximately twice that which was necessary. Based on criteria utilized in this study, over half of all digitalis glycoside serum assays requested were not indicated. The reliability of these criteria was demonstrated by other findings: a) none of the assays receiving a clinical evaluation score of less than 10 were reported above 2.1 ng/ml (Figure 2). This is not surprising since the criteria was purposely weighted to support any suspicion of toxicity, b) none of the assays receiving a clinical evaluation score of less than 10 resulted in dosage adjustment recommendations that differed from an accepted theoretical method using assay results. Reliability is further supported by the close agreement with the findings of Slaughter et al.[26] who reported that 49 percent of 145 cases had inappropriate indications for the use of serum assays. Slaughter et al.[26] also reported that 86 percent of assays were performed at steady state making 14 percent of their assay results uninterpretable on this basis according to Jisalo.[23] Steady state was not evaluated in this study.

Measurement of assays before the recommended time interval is similar in both studies. Slaughter et al. showed that seven percent of assays were obtained before a six hour interval versus 13 percent observed in the present study. Closer examination, however, reveals a much larger deficiency in this area. Most assay requests in the present study were written "digoxin level," "digoxin level tomorrow" or "digoxin level

FIGURE 2

Digoxin Concentration of Samples from Patients That Received Clinical Evaluation System Scores Within Normal Limits



today." Only one physician specified a particular time interval and in this case, it was for only one patient. In addition, quiz results show that only 20 percent of the residents, who were responsible for 70 percent of the assays ordered, knew when a digoxin level reached the beta phase of elimination and therefore became the earliest time that a serum sample could be drawn to obtain meaningful assay results.[23] This suggests that the 13 and 7 percent error rates are actually underestimations of an error rate which would have occurred without the "protection" afforded by the combined systems of the laboratory blood drawing team and the medication administration system of the nursing staff. The blood drawing team routinely collects samples before the administration of all early morning medications, unless specifically ordered otherwise. Nursing staff concurrently administers all "once daily" medications at 9 a.m. Consequently, there is a tendency for the large majority of digoxin serum samples to be obtained at trough levels just prior to the next dose. Data results may thus be mistakenly interpreted as an area of expertise when in fact such results may be due to a predetermined protocol.

Of the assays that were indicated in this study, 43 percent were followed by inappropriate adjustments in therapy. The reasons for which ideal adjustments in therapy differed from that which patients actually received appear in Table X. The overall number of inappropriate adjustments that patients would have received with proper clinical assessment without the aid of digoxin assay information (39 percent) does not appear to be different from what they actually received when the assay was available. This suggests that the assay may have actually contributed to confusion regarding assay interpretation and ultimate patient therapy.

Slaughter et al. reported 36 percent inappropriate adjustments by their criteria but made no additional comparisons with recommendations made on the basis of clinical assessment only. The 43 percent reported in the present study include only those adjustments that were or were not made within 12 to 24 hours after the initial order as methods indicated. This time limit may account for the higher incidence of inappropriate adjustments observed in this study when compared to the results of Slaughter's group who followed their patients for 48 hours.

TABLE X: Explanation For Differences Between Ideal Adjustment Recommendations and Actual Dosage Adjustments Received

Adjustment in Therapy Recommended by Ideal Method	Number of Patients	Explanation for Adjustment Recommendation
Increase	6	CES* subtherapeutic (≤ -10), assay maximum 1.1 ng/ml. Patients needed increase or restart of previous dosage.
Decrease	6	CES* toxic (≥ 10), assay minimum 2.2 ng/ml. Trial decrease in dosage is indicated.
	6	CES* toxic (18-20), assay 1.7-2.1 ng/ml. Trial decrease in dosage is indicated.
No change	5	CES* WNL† (-9-+9), assay 0.5-2.1 ng/ml. Patients had no clinical problems and required no change.
	1	CES* 18, assay 0.8 ng/ml. Toxicity rare at this level.

*CES = Clinical Evaluation System score
†WNL = Within Normal Limits

Errors made in assay utilization, assay interpretation and therapy outcome are ultimately passed on to patients in terms of costs, discomfort and length of hospital stay. This is clearly demonstrated by a case

in the present investigation. A 72 year old female with severe chest pain was admitted in order to rule out myocardial infarction. Iatrogenic digitalis toxicity in the form of ventricular fibrillation, severe hallucinations, confusion, stupor, fatigue, nausea and vomiting marked this patient's complicated hospital course. During the course of the present study, 20 digoxin assays were obtained, costing the patient nearly $600.00 for digitalis glycoside assay service alone. Three of these assays were obtained less than six hours after the previous dose and were therefore uninterpretable. Seventeen of the assays were unnecessary. Seven scored in the non-toxic range, while the other 10 were obtained on a daily basis and therefore added nothing to the knowledge of the patient's status or to the benefit of the patient in terms of therapy that she may not have otherwise received.

The knowledge of half-life and the understanding of its use are basic concepts necessary for proper clinical assessment and therapy. Results of the physician quiz and clinical performance suggest that clinicians are generally not aware of the importance of pharmacokinetics and the impact that this may have on clinical assessment and outcome of patient therapy.

The use of objective methods for dosing digitalis glycosides has been shown to effectively decrease the incidence of adverse effects.[30,31] In light of this, the use of clinical judgment as the basis for dosage adjustment of digitalis glycosides, such as that seen with all of the physicians in this study may be inappropriate. It should be noted, however, that not all physicians ordering digitalis glycosides in this hospital, but only those ordering blood levels, were included in this study.

In conclusion, it would seem that under the conditions of the present study, the following were shown: a) digitalis glycoside serum assays were overused which may well reflect overuse on a wider scale; b) a large number of digitalis glycoside serum assays obtained was not indicated and a greater reliance on clinical parameters may be necessary when evaluating patients on digitalis glycosides; c) recognition of the importance and implications of proper timing for serum sampling is lacking and may result in misinterpretation of assay results; d) a large percentage of indicated assays are followed by inappropriate dosage adjustments; e) patient costs were unnecessarily high during this period and may be twice those which are actually necessary on an annual basis in this hospital; and f) physician knowledge and understanding of digitalis glycoside assay utilization appears to be deficient and may be related to suboptimal results observed in this study.

Physician education and pharmacokinetic consultative services may be an answer to this problem. Impact of such consultative services has been studied and appears to be effective in improving overall patient care.[29] Further research in this area is needed.

APPENDIXES

APPENDIX A

Patient Data Collection

Date:

PATIENT INFORMATION:

Patient Code Number	Age:
Sex:	Admission Date:
Weight:	Height:
Lean-Body Weight:	Theoretical Dose:

LAB DATA (within 24 hours unless otherwise specified):

Potassium:	Calcium:
pH:	Serum creatinine/BUN:
pO_2:	Magnesium:

Problem List: In Chart Not in Chart (listed for cardiologists)
Digoxin Indication:
Current Digoxin Regimen:
Most Recent Dose:
Most Recent Dose Change:
Current Medications: In Chart Not in Chart (listed for cardiologists)
Past Medication History: In Chart Not in Chart

EVIDENCE FOR TOXICITY:

Gastrointestinal Symptoms:

Anorexia ____ kgs. over ____ time	Nausea
Vomiting	Diarrhea
Abdominal Pain	Bloating
Other Describe:	

Central Nervous Systems Symptoms:

Fatigue	Extreme Weakness
Drowsiness	Apathy
Confusion	Insomnia
Restlessness	Hallucination
Other Describe:	

Visual Symptoms:
Altered color vision - indistinct or dull

EVIDENCE FOR SUBTHERAPEUTIC EFFECT

Symptom Regression:

Weight Gain	Edema
Orthopnea	Urinary Frequency
Dyspnea on Exertion	Shortness of Breath
Arrhythmia Return	Other Describe:

Compliance History:
Excellent Good Fair Poor

APPENDIX B

Clinical Evaluation Point System

RULE: Clinically Toxic equal 10 points minimum.
Clinically Subtherapeutic equal -10 points maximum.

POINTS	EVIDENCE
10	Overdose (acute). Must be documented or highly suspected.
10	ECG. Must have at least one rating of three or four by at least one cardiologist.
10	Gastrointestinal. Must have at least four symptoms.
10	Central Nervous System. Must have at least four symptoms.
10	Visual.
10	Serum creatinine doubled over any period of time since most recent dosage change.
10	Creatinine Clearance. Must show change of at least 50 percent since most recent dosage change (-10 points if such change favors improved elimination).
10	Switching from digitoxin to digoxin.
-10	Symptoms of regression. Must have more than one symptom.
9	Gastrointestinal. Must have less than four symptoms.
9	Central Nervous System. Must have less than four symptoms.
-9	Symptoms of regression. One symptom
1	Potassium. Must be less than or equal to 3.0
1	Calcium. Must be greater than or equal to 10.2
1	pH. Must be greater than or equal to 7.5
1	Magnesium. Must be less than or equal to 1.9.
1	pO_2. Must be less than 60.0 without history of chronically low pO_2.*
1	No other possible underlying disease to explain symptoms.
1	Creatinine greater than 2.0 and age greater than 70.
1	Theoretical Dose = Present dose - (0.1 mg. or more)
1	Theoretical Dose = Present dose + (0.9 mg. or more).
-1	Compliance. Poor only. (Missing greater than three doses per month).

*pO_2 adjusted for altitude.

APPENDIX C

PHYSICIAN QUIZ

1. What method of Assay is used for digitalis determination of serum levels in this hospital?
(Ans. Radioimmunoassay (RIA) - one point)

2. What is the normal therapeutic range for digoxin?
(Ans. 0.7 ng/ml to 2.0 ng/ml - one point. Accepted 0.5 to 2.2 ng/ml)

3. What is generally thought to be a toxic level?
(Ans. Greater than 2.2 ng/ml depending on disease state being treated - one point. Accepted greater than 2.0 ng/ml OR depends on disease being treated.)

4. What is the half-life range for digoxin? What is the mean half-life?
(Ans. 24 to 48 hours range, 36 hours mean - one point. Accepted 1-3 days range - ½ point, 30-40 hours mean - ½ point.)

5. When is the earliest time after an oral dose that a digoxin level may be drawn to obtain meaningful results?
(Ans. after 8 hours - one point. Accepted after 6 hours.)

6. When are digoxin and digitoxin levels indicated?
(Ans. Clinical suspicion of toxicity or non-compliance, history of unstable renal condition - one point. Accepted any single indication - ½ point, any 2 indications - one point.)

7. How much do digoxin and digitoxin serum levels cost in this hospital? Are there holiday rates?
(Ans. Digoxin $17.50 normal, $27.50 holiday/off-hours - one point. Accepted $15-30.)

8. What are the most common symptoms of digitalis toxicity?
(Ans. Gastrointestinal, cardiac and central nervous system - one point. Accepted any 2 - ½ point, all 3 - one point.)

9. What other lab data do you need when evaluating toxicity of digitalis glycosides?
(Ans. EKG, serum creatinine/blood urea nitrogen, potassium, calcium, pO2 - one point. Accepted any 2 - ½ point, more than 2 - one point.)

10. What method do you use for calculating a maintenance dose for your patients?
(Ans. Any nomogram or mathematical method - one point.)

APPENDIX D

PHYSICIAN TELEPHONE QUIZ EXPLANATION

Hello, Dr. _____. This is Jack Wilson. I'm a Doctor of Pharmacy Candidate from the University of Utah, and I am currently working with the laboratory here at Holy Cross on a project designed to improve the dissemination of information with regard to pharmacokinetic interpretation and the utilization of the many drug serum levels that are being done in this hospital.

What I would like to do is ask you a few questions concerning one of the drugs for which serum levels are commonly ordered. This will appear as an entirely anonymous report and it should take only a few moments.

Would you be willing to help us out?

APPENDIX E

Data Summary

Patient I.D. Number	Patient Age	Patient Sex	Assay Code No.	Physician Code No.	Physician Rank	Percent Availability of Evaluation Factors	ECG Scores, A/B	Clinical Evaluation System Score			Assay Results	Time Interval	Actual Change in Therapy Post Assay	Ideal Change in Therapy Post Assay	Indicated Change in Therapy Without Assay	Patient Cost
								Toxic	WNL	Sub-therapeutic						
1	65	M	1	1	R	73				-10	1.5	4	-	↑	↑	17.50
2	86	M	2	2	P	68			0		0.8	23	-	-	-	17.50
3	75	F	3	1	R	73	1/3	19			2.1	23	-	↓	↓	17.50
4	79	F	4	3	P	82	3/4	10			1.8	24	-	↓	↓	17.50
5	88	M	5	4	R	18	2/3	10			42.0	2	-	-	↓	25.00
6	72	F	93	9	R	73			0		0.8	24	-	-	-	25.75
			101	9	R	73			0		0.7	15	-	-	-	25.75
			8	9	R	82	1/1	30			4.8	2	↓	↓	↓	25.75
			26	9	R	55		19			4.6	3	↓	↓	↓	17.50
			31	9	R	82		28			2.1	29	-	-	-	17.50
			32	10	R	91	1/1		9		1.9	3	-	-	-	44.10
			41	9	R	64		18			>5.0	22	-	-	-	25.75
			44	9	R	55		19			4.4	46	-	-	-	25.75
			46	9	R	55		19			3.8	72	-	-	-	35.75
			49	9	R	64		10			3.7	96	-	-	-	35.75
			57	9	R	64		10			2.6		-	-	-	35.75
			58	9	R	64		10			2.9		-	-	-	25.75
			62	9	R	45		19			3.0	6	-	-	-	25.75
			63	9	R	73	1/1	19			2.9	22	-	-	-	25.75
			71	9	R	64		10			2.3	46	-	-	-	25.75
			79	9	R	64		10			2.2	>>8	-	-	-	35.75
			83	9	R	64			9		1.6	24	-	-	-	25.75
			86	9	R	73			0		2.1	>>8	-	-	-	25.75
			87	9	R	73			0		2.0	>>8	-	-	-	25.75
			90	9	R	73			0		1.2	>>8	-	-	-	25.75

APPENDIX E

Data Summary (con't)

Patient I.D. Number	Patient Age	Patient Sex	Assay Code No.	Physician Code No.	Physician Rank	Percent Availability of Evaluation Factors	ECG Scores, A/B	Clinical Evaluation System Score			Assay Results	Time Interval	Actual Change in Therapy Post Assay	Ideal Change in Therapy Post Assay	Indicated Change in Therapy Without Assay	Patient Cost
								Toxic	WNL	Sub-therapeutic						
7	62	F	6	14	P	82	1/1		9		1.5	24	-	-	-	25.75
8	57	F	7	15	P	77	1/1		1		0.8	23	-	-	-	25.75
9	63	M	9	20	R	55				-10	2.8	2	-	-	↑	25.75
10	68	F	10	8	R	50		10			0.8	36	↑	↑	↓	44.10
11	69	M	11	12	R	50			0		1.9	5.5	↑	-	-	25.75
			37	12	R	64		18			2.7	5.5	-	↓	↓	25.75
12	69	M	12	5	R	64	1/2		9		0.7	23	-	-	-	17.50
			39	5	R	82	1/2		1		0.6	27	-	-	-	25.75
			43	5	R	41			0		0.4	22	-	-	-	25.75
13	64	F	13	6	R	73	1/1	18			0.5	23	-	-	↓	17.50
			107	6	R	36			0		1.7	21	-	-	-	17.50
14	79	F	14	7	P	45			0		1.4	23	-	-	-	17.50
			54	7	P	32			9		1.0	22	-	-	-	25.75
15	71	F	15	8	R	82	1/2			-10	0.5	23	-	↑	↑	17.50
16	68	M	16	9	R	91	1/1			-11	1.5	8.5	-	-	↑	25.75
17	72	F	17	10	R	55			0		1.1	7	-	-	-	25.75
18	90	F	18	11	R	55	3/3	20			1.5	96	↑	↑	↓	17.50
			27	16	P	82			0		0.8	144	-	-	-	17.50
19	78	M	19	12	R	64		18			0.9	23	-	-	↓	25.75
20	75	F	20	10	R	73	1/1	18			0.8	?	↓	-	↓	25.75
			29	10	R	55			1		1.7	23	↓	-	-	17.50
21	66	F	21	10	R	82	1/1			-10	1.9	23	-	-	↑	17.50
22	78	F	22	12	R	82	1/1		9		1.4	13	-	-	-	17.50
23	85	F	23	13	R	91	1/1	10			1.9	23	-	-	↓	17.50
24	70	M	24	14	P	73	1/1		9		2.1	24	-	-	-	17.50
25	72	F	25	15	P	55	2/2		1		1.6	17	-	-	-	17.50

APPENDIX E

Data Summary (con't)

Patient I.D. Number	Patient Age	Patient Sex	Assay Code No.	Physician Code No.	Physician Rank	Percent Availability of Evaluation Factors	ECG Scores, A/B	Clinical Evaluation System Score			Assay Results	Time Interval	Actual Change in Therapy Post Assay	Ideal Change in Therapy Post Assay	Indicated Change in Therapy Without Assay	Patient Cost
								Toxic	WNL	Sub-therapeutic						
26	74	F	28	6	R	64	1/2	20			3.1	25	-	↓	↓	25.75
			97	6	R	50	1/1	18			2.1	22	-	↓	↓	25.75
27	90	M	30	6	R	82	1/1			-11	0.9	24	↑	↑	↑	25.75
28	66	M	33	10	R	50	3/2		0		0.6	23	-	-	-	25.75
29	62	M	45	7	P	55				-10	0.7	168	-	↑	↑	44.10
30	59	F	35	12	R	73	1/1		9		0.9	23	-	-	-	25.75
			103	19	P	59		20			1.7	29	↑	↓	↓	17.50
31	60	F	36	10	R	82	2/2		9		0.5	9	↑	-	-	17.50
32	64	M	40	18	P	73			9		1.0	9	-	-	-	25.75
33	62	F	42	19	P	36				-10	0.1	24	-	↑	↑	25.75
34	60	M	47	6	R	68	1/1	10			2.8	24	-	↓	↓	35.75
			59	6	R	82	3/3	19			0.6	96	↑	↑	↑	25.75
35	54	M	48	18	P	73	1/1	18			0.7	16	-	-	↓	25.75
36	47	M	50	9	R	73	1/1			-10	1.1	23	-	↑	↑	25.75
37	85	M	53	20	P	27	1/1		0		1.4	22	-	-	-	44.10
38	85	F	55	6	R	50	1/1		0		0.6	23	-	-	-	25.75
			61	6	R	45			9		1.6	22	-	-	-	25.75
39	88	F	56	21	P	73	1/1		1		0.9	22	-	-	-	25.75
40	57	F	60	12	R	68	3/2	19			1.4	24	↑	↑	↓	25.75
41	64	M	64	18	P	73			9		1.4	22	-	-	-	25.75
42	88	M	65	12	R	73	3/3	10			0.7	8.5	-	-	↓	25.75
43	66	M	66	8	R	68	1/1	10			3.0	8	↓	↓	↓	25.75
44	64	M	69	14	P	77	3/3	10			1.2	?	-	-	↓	25.75
45	81	M	68	15	P	64		10			2.8	23	-	↓	↓	25.75
46	67	F	70	6	R	73	1/1		9		1.9	21	-	-	-	25.75

APPENDIX E

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								Toxic	WNL	Sub-therapeutic						
47	53	F	73	22	P	55	3/4	10			0.7	80	↑	↑	↓	25.75
48	35	F	77	12	R	82	1/2		9		0.9	1.5	-	-	-	25.75
49	86	M	75	23	P	77	3/3	10			0.2	?	-	-	↓	25.75
50	87	F	76	5	R	82		21			3.5	4	-	↓	↓	25.75
			81	5	R	73		30			3.2	25	-	↓	↓	25.75
51	79	F	80	6	R	68	1/1		0		1.0	?	-	-	-	25.75
52	79	F	82	24	P	73	1/2		9		0.5	4	-	-	-	25.75
53	77	M	84	10	R	68		20			1.9	23	↑	↓	↓	25.75
54	88	F	85	12	R	68	1/2		9		1.9	24	-	-	-	25.75
55	78	F	88	19	P	50	1/1	10			$\frac{1.6}{32}$	4	-	-	↓	65.75
			98	19	P	41		10			14.5	96	-	↑	↑	40.00
56	90	F	89	25	P	77	3/3	19			2.5	23	↓	↓	↓	25.75
57	75	M	92	18	P	45			9		1.5	?	-	-	-	25.75
			96	25	P	64	1/1		0		1.8	72	-	-	-	25.75
58	72	M	94	9	R	73	1/1		0		1.2	8.5	-	-	-	25.75
59	72	F	99	26	P	73	1/3	10			0.4	22	-	-	↓	25.75
60	43	F	100	29	P	64			0		0.9	23	-	-	-	25.75
61	69	M	102	12	R	73	1/1		0		1.2	23	-	-	-	25.75
62	73	F	104	8	R	64			9		15.5	144	↑	↑	↑	25.00
63	60	F	105	27	P	55			0		0.9	22	↑	-	-	17.50
64	79	F	106	21	P	45			0		2.1	5	↓	-	-	17.50
65	49	F	109	6	R	68	2/3	19			2.0	24	↑	↓	↓	25.75
66	74	M	110	9	R	62				-10	0.2	24	-	↑	↑	25.75
67	72	M	111	9	R	91	3/3	20			3.2	24	↓	↓	↓	25.75
68			108	9	R	73		10			1.2	23	-	-	↓	25.75

EVALUATION OF PHYSICIAN UNDERSTANDING

Physician Code Number/Rank	SCORE Question Number 1	2	3	4	5	6	7	8	9	10	OVERALL SCORES (%)
1/R	-	1	1	-	-	½	-	1	1	-	45
2/P	-	1	1	-	1	1	-	1	-	-	50
3/P	NOT INTERVIEWED										-
4/R	1	1	1	1	-	½	1	½	1	-	70
5/R	-	-	1	-	-	1	-	½	½	-	30
6/R	1	1	1	½	-	½	-	½	1	-	55
7/P	-	1	1	-	-	-	-	1	-	-	30
8/R	1	1	1	-	-	½	-	1	½	-	50
9/R	-	1	1	-	1	1	-	½	½	-	50
10/R	1	1	1	½	-	½	-	½	-	-	45
11/R	-	1	1	-	1	½	-	1	1	-	55
12/R	-	1	1	½	-	½	-	-	1	-	40
13/R	1	1	1	1	-	½	1	1	1	-	75
14/P	-	1	1	½	1	1	1	½	1	-	70
15/P	1	1	1	-	1	1	1	½	½	-	70
16/P	-	1	1	-	-	½	-	½	-	-	30
17/P	NOT INTERVIEWED										-
18/P	-	1	1	-	1	1	-	1	½	-	55
19/P	1	1	1	-	1	1	-	½	1	-	65
20/P	-	1	1	-	1	1	1	1	-	-	60
21/P	-	1	1	-	1	½	1	1	½	-	60
22/P	-	1	1	-	-	-	-	½	1	-	35
23/P	1	1	1	-	1	1	1	1	1	-	80
24/P	NOT INTERVIEWED										-
25/P	-	½	1	-	-	½	-	1	1	-	40
26/P	?	?	?	?	UNCO-OPERATIVE						0
27/P	NOT INTERVIEWED										-
	8/23	20.5/23	22/23	4/23	10/22	14.5/22	7/22	16/22	14/22	0/23	
Residents	50	90	100	35	20	60	20	65	75	0	51.5
Private	23	88	92	4	67	71	42	79	54	0	49.6
MEAN SCORES	40	89	96	17	45	66	32	73	64	0	50.4

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